Causality Analysis using Resting State BOLD fMRI in Normal and Ischemic Rat Brains

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ABSTRACT Previously, Friston et al. defined functional connectivity as the temporal correlation of neurophysiological signals (e.g., BOLD, PET or EEG) between two brain regions.(1) Significant correlations between these brain regions using stimuli that elicit responses in multiple brain regions may implicate various functional connections. In parallel to task-induced activities, resting state low-frequency cerebrovascular fluctuations also provide insights into baseline vascular physiology and functional connectivity in the absence of cognitive tasks. Previously, Biswal et al. showed using fMRI that the spontaneous low-frequency hemodynamic oscillations are spatially synchronous, which was interpreted as evidence for active neural connectivity between discreet brain regions during resting state.(2) In this study, using both normal and ischemic rat models, we demonstrated that specific connective relationships can be extracted from resting state fMRI BOLD time courses collected from various brain regions. In particular, we used Granger analysis to evaluate directional connectivity (i.e., causality) between two different systems (time series), addressing i) thalamic influences over sensorimotor cortices, ii) bidirectional connectivity between bilateral thalamus and sensorimotor cortices, and iii) significant alteration in Granger causality due to ischemic damage between these brain regions.(3) In stroke rats, the degree of alterations in directional connectivity correlated with the magnitude of task-induced responses (i.e., electrical forelimb stimulation) in ipsilesional sensorimotor cortices.

MATERIALS AND METHODS Both resting state and task-induced fMRI activities were acquired using echo planar imaging (EPI) pulse sequences at 9.4 T for normal healthy Sprague-Dawley rats (n=3: 275~325g) and for rats with transient occlusion (90 min) of middle cerebral artery (MCAO). For stroke rats, fMRI was performed 1 day (n=2) and two months (n=3) following the ischemic attack. Mechanically-ventilated rats were anaesthetized with the continuous infusion of alpha-chloralose and pencuronium during the fMRI session. Functional changes in resting state BOLD signals were acquired using gradient EPI sequence (9 slices: TR/TE = 3700/15 ms) while task-induced BOLD fMRI activations were investigated by electrically stimulating bilateral forelimbs. Anatomically-selected regions of interest (ROI) were used to obtain fMRI time series in the thalamus and sensorimotor cortices. Prior to the temporal analysis, each time course was detrended to the second order and bandpass-filtered between 0.02 and 2 Hz. For the connectivity analysis, we used the Granger causality method, as previously proposed by Goebel et al.,(3) to evaluate the mutual influence of time-series collected from one ROI (i.e., anatomically pre-defined bilateral thalamic nuclei and sensorimotor cortices) on another.

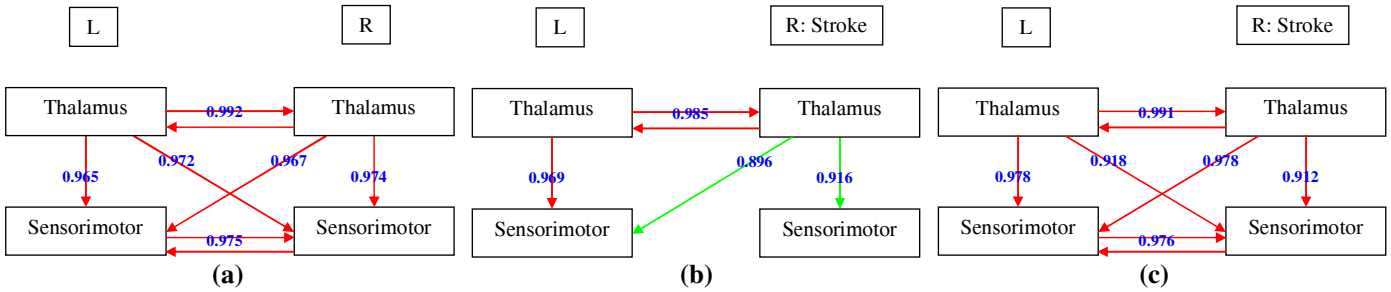

Figure 1. Dynamic connectivity between left and right thalamus and sensorimotor cortices in normal **(a)** and stroke rats (1 day **(b)** and 2 months **(c)** following 90 min MCAO): Blue characters – mean cross correlation coefficient (p<0.05) and red arrows - directional connectivity obtained using Granger Analysis (Red arrow - p<0.05 and Green arrow - p<0.10).

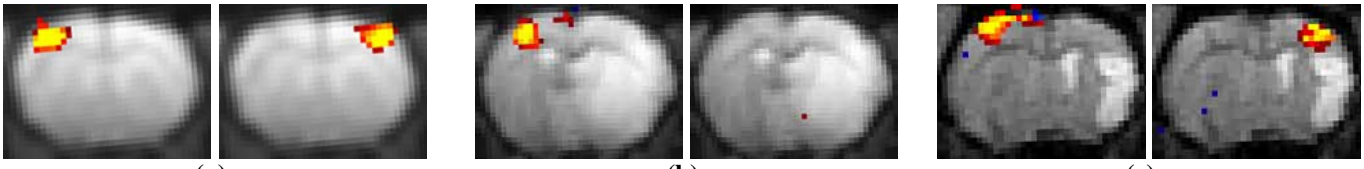

Figure 2. Representative task-induced fMRI activation maps using electrical forelimb stimulation in a normal rat **(a)** and stroke rats on 1 day **(b)** and 2 months **(c)** after the MCAO: left and right panels – stimulation of unaffected and affected limbs, respectively.

RESULTS AND DISCUSSION The Granger analysis permits the evaluation of the connective strength and directional influence between discrete brain regions. Schematic diagrams demonstrating dynamic connectivity between the thalamus and sensorimotor cortices in resting state rat brains as a result of Granger analysis are shown in Figure 1. Significant mutual influences were found between the bilateral thalamus and bilateral sensorimotor cortices in normal healthy rats (n=3). Moreover, the results using normal rats (Figure 1a) indicated unidirectional influences of thalamus on sensorimotor regions. The calculated cross-correlation coefficient also showed that resting state time courses are significantly correlated between selected brain regions. On the other hand, the directional connectivity was, in general, significantly affected by transient MCAO at early stages of stroke progression (Figure 1b); however, the reduced connectivity was restored in the later phase (Figure 1c). Such stroke-affected changes in resting state causality during stroke progression strongly correlated to time-dependent alterations in the task-induced activation magnitude measured in the ipsilesional sensorimotor cortex (Figure 2). The results demonstrate the potential importance of resting state low-frequency activity and directional connectivity as predictive markers of task-induced fMRI activation and further warrant detailed future studies in correlation with recovery processes.

REFERENCES

1. Friston, K. J., Frith, C. D. & Frackowiak, R. S. (1993) *Proc Biol Sci* **254,** 47-54.
2. Biswal, B., Yetkin, F. Z., Haughton, V. M. & Hyde, J. S. (1995) *Magn Reson Med* **34,** 537-41.
3. Goebel, R., Roebroeck, A., Kim, D. S. & Formisano, E. (2003) *Magn Reson Imaging* **21,** 1251-61.